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Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy is an effective new treatment for hematologic malignancies. Two CAR T-cell products are now approved for clinical use by the U.S. FDA: tisagenlecleucel for pediatric acute lymphoblastic leukemia (ALL) and adult diffuse large B-cell lymphoma subtypes (DLBCL), and axicabtagene ciloleucel for DLBCL. CAR T-cell therapies are being developed for multiple myeloma, and clear evidence of clinical activity has been generated. A barrier to widespread use of CAR T-cell therapy is toxicity, primarily cytokine release syndrome (CRS) and neurologic toxicity. Manifestations of CRS include fevers, hypotension, hypoxia, end organ dysfunction, cytopenias, coagulopathy, and hemophagocytic lymphohistiocytosis. Neurologic toxicities are diverse and include encephalopathy, cognitive defects, dysphasias, seizures, and cerebral edema. Our understanding of the pathophysiology of CRS and neurotoxicity is continually improving. Early and peak levels of certain cytokines, peak blood CAR T-cell levels, patient disease burden, conditioning chemotherapy, CAR T-cell dose, endothelial activation, and CAR design are all factors that may influence toxicity. Multiple grading systems for CAR T-cell toxicity are in use; a universal grading system is needed so that CAR T-cell products can be compared across studies. Guidelines for toxicity management vary among centers, but typically include supportive care, plus immunosuppression with tocilizumab or corticosteroids administered for severe toxicity. Gaining a better understanding of CAR T-cell toxicities and developing new therapies for these toxicities are active areas of laboratory research. Further clinical investigation of CAR T-cell toxicity is also needed. In this review, we present guidelines for management of CRS and CAR neurotoxicity.

Keywords

Chimeric antigen receptor (CAR) T cells; Hematologic malignancies; Toxicity

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1. Introduction to CAR T-cell therapy

A chimeric antigen receptor (CAR) is a fusion protein comprised of an antigen recognition moiety and T-cell signaling domains [1–6]. Clinical trials of CAR T cells targeting the B-cell marker CD19 have shown clear efficacy in multiple hematologic malignancies, including ALL [7–13], chronic lymphocytic leukemia (CLL) [14–17], and non-Hodgkin lymphoma (NHL) [18–28]. CAR T cells targeting B-cell maturation antigen (BCMA) have demonstrated activity in multiple myeloma (MM) [29–31]. CAR T cells are now also being investigated in clinical trials of Hodgkin lymphoma [32,33] and in some solid tumor malignancies [34–37]. The U.S. FDA has approved the anti-CD19 CAR T-cell product tisagenlecleucel for multiply relapsed or refractory pediatric ALL [38]. Tisagenlecleucel and axicabtagene ciloleucel are both FDA approved for diffuse large B-cell lymphoma (DLBCL) subtypes following 2 or more prior lines of therapy [39,40]. With further approvals of CAR T-cell products expected for use in hematologic malignancies, CAR T cells are anticipated to be used in an increasing number of patients.

While CAR T-cell clinical trials have shown positive results, severe toxicities are possible and can be life-threatening [7–9,15,18–22,29, 30,41–44]. The most common severe toxicity is a systemic inflammatory response termed cytokine release syndrome (CRS), which is characterized by high fevers, sinus tachycardia, hypotension, hypoxia, depressed cardiac function, and other organ dysfunction [7–9,14,15,18–20,22,25,29,41–43]. CRS is thought to be caused by the release of inflammatory cytokines from the CAR T cells and other immune cells [7–9,14,18–21,42]. CAR T cells can also cause neurologic toxicity, a heterogeneous and poorly understood disorder with variable clinical presentation and severity [7–9,14,15,19–22,41]. Toxicities are usually reversible and resolve on their own in most cases, though severe cases may require intensive care [7,9,14,15,20,25,41] and immunosuppressive therapy [7,8,11,25,30,41–43]. Deaths due to both CRS [9,13,15,25] and neurologic toxicity [9,15,26] have been reported, highlighting the gravity of these syndromes and the critical nature of appropriate intervention.

Here we describe the diversity of toxicities that have been reported following infusion of CAR T cells, review existing toxicity grading systems and management strategies, and present our own treatment approach for these patients. Our management recommendations are based on our institutional experience, are limited to adult patients, and may conflict with other guidelines developed by other institutions or presented for specific CAR T-cell products.

2. Clinical manifestations of CAR T-cell toxicity

The first presenting symptom of CRS is usually fever [9,14,20,42], which can occur hours to several days following cell infusion [9,11]. In a clinical trial of anti-CD19 CAR T cells for ALL, patients initially developed fever as early as the day of infusion and as late as 9 days after cell infusion [9]. Similarly, in our experience, patients usually experience the first signs of CRS within 14 days following CAR T-cell infusion, though infrequent cases of delayed CRS are possible. CRS in our experience usually peaks and starts to resolve within 7 days. Following the initial fever, patients may then develop sinus tachycardia, hypo-tension,

depressed cardiac function, and hypoxia [7–9,11,14,18–22, 29,30,45]. Hypotension may necessitate vasopressor support [7,9,12,25,29,30,46,47]. Patients may develop dyspnea and hypoxia due to pulmonary edema in the setting of a capillary leak syndrome caused by circulating cytokines [7,8,11,21,22]. In severe cases, patients may require mechanical ventilation due to respiratory failure [7,12,21,46,47]. Other constitutional symptoms that may occur include fatigue, headaches, and myalgias [11,14,18,19,41]. CAR T-cell toxi-cities are listed in Table 1.

CAR T cells can cause multiple end-organ toxicities, which are reversible in most cases. In addition to sinus tachycardia, other arrhythmias [11,20,21,29,30], QT prolongation [8], troponinemia [29,48], and decreased left ventricular ejection fraction [8,20–22, 30,48] have been reported. Transient increases in hepatic enzymes and bilirubin have been observed [8,18,21,22,29,30,45,47,49]. Similarly, renal insufficiency suggested by a transient rise in serum creatinine may occur [8,18,19,22,29,47]. In severe instances, patients have required temporary hemodialysis support [22,30]. Various electrolyte derangements can occur, including hyponatremia [8,11,21,22,29,30], hypokalemia [8,45], and hypophosphatemia [8,22,29,30,45]. Tumor lysis syndrome has been observed [14], even in patients receiving no conditioning chemotherapy prior to their CAR T-cell infusion [48]. Elevation in creatine phosphokinase, suggesting inflammatory muscle damage, has been reported [8,29,30,45]. While the above end organ toxicities are almost always reversible, maintaining good end organ function is especially a priority for patients with ALL for whom allogeneic stem cell transplant is planned once a remission is achieved following CAR T-cell therapy.

Multiple hematologic toxicities may occur following CAR T-cell infusion. Conditioning chemotherapy regimens contribute to the development of anemia [8,21,22,29,49], thrombocytopenia [8,21,22,29, 30], and neutropenia [8,11,14,20–22,29,30], though all have been reported in absence of chemotherapy conditioning as well [45]. Prolonged duration of cytopenias is possible [12,30]. Because anti-CD19 CAR T cells deplete normal B cells as well as malignant cells, B-cell aplasia and hypogammaglobulinemia are common following anti-CD19 CAR T-cell infusions; patients sometimes receive intravenous immunoglobulins to address this [8,9,14,18,20–22,45,50]. Prolongation in the prothrombin time (PT) [7], partial thromboplastin time (PTT) [7,8,21,29,30,45], decreased fibrinogen [7,29,30], and disseminated intravascular coagulation [9] have occurred. Hemorrhagic events following CAR T-cell therapy have resulted in patient deaths [12,20,22,51], though these events had multifactorial causes, and the contribution of the CAR T-cell infusions was unclear. Hemophagocytic lymphohistiocytosis (HLH) has been described during CRS [14,25,46]. The mechanism of post-CAR T cell HLH is not well understood, and this form of secondary HLH may represent the most severe progression of CRS. Diagnostic criteria for CAR T-cell related HLH have been proposed [43]. To fulfill these criteria, an elevated ferritin of > 10,000 ng/mL is required, along with at least two organ toxicities, including presence of hemophagocytosis in bone marrow or organs, or at least grade 3 transaminitis, renal insufficiency, or pulmonary edema [43].

CAR T cells may cause certain neurologic effects, sometimes referred to as CAR T-cell related encephalopathy syndrome, or CRES. Here, we will refer to these effects as “neurologic toxicities,” or “neurotoxicities.” Neurologic toxicities caused by CAR T cells

are diverse and do not localize to one region of the central nervous system (CNS). Patients may experience delirium [7,9,11,14,19–22,25,52], hallucinations [7,14,21,22], cognitive defects [25], tremors [8,20–22,52], ataxia [8,19,21], dysphasias [7,8,19–22,25,52], nerve palsies [19], focal motor or sensory deficits [21,52], myoclonus [19,52], somnolence [21,22,52], obtundation [11,19], or seizures [7,9,12,21,52]. Intubation and mechanical ventilation may be required for airway protection in obtunded patients [9,11,21]. Cerebral edema has led to deaths in a small number of patients [15,53]. Neurologic toxicities may occur simultaneously with signs of CRS such as hypotension, but neurologic toxicities may occur in patients not having typical signs of CRS or after CRS abates [7,9]. Neurologic toxicities have been reported to occur as early as the day following CAR T-cell infusion [9], to the third or fourth week after CAR T-cell infusion [43], demonstrating a highly variable course. Close monitoring for neurologic toxicity is required throughout the treatment course.

Patients receiving CAR T-cell infusions may be significantly immunosuppressed due to conditioning chemotherapy and their underlying malignancy and are therefore susceptible to infections, including viral, bacterial, and invasive fungal infections [54,55]. Deaths have been reported due to infections in patients participating in clinical trials of CAR T cells [14,18,54,55]. Patients with ALL, more lines of prior therapy, receiving a higher cell dose, and experiencing higher grade CRS may be at greater risk for infection [54,55]. These complications highlight the importance of monitoring patients who are febrile following CAR T-cell infusion for any sign of infection that may be concurrent with CRS.

3. Factors contributing to CAR T-cell toxicity

CRS is an inflammatory syndrome caused by multiple cytokines produced by the CAR T cells themselves and by other cells. Cytokines and inflammatory markers associated with more severe CRS include C-reactive protein (CRP), ferritin, interferon (IFN)-ϒ, interleukin (IL)-1, IL-2, soluble IL2Rα, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, granzyme B, granulocyte/macrophage colony stimulating factor (GM-CSF), soluble gp130, macrophage inflammatory protein-1α (MIP-1α) and monocyte chemoattractant protein-1 (MCP-1) [7–9,11,12,14, 19,20,25,42,46]. The pathogenesis of neurologic toxicity remains poorly understood, though recent advancements have been made. Severe neurologic toxicity occurs almost exclusively in patients who develop CRS and usually occurs after the first fever [52,56]. Neurologic toxicity can occur at the same time as CRS, but in some instances may not occur at the same point, but instead before CRS or days later [52,56]. Higher neurologic toxicity grade has been observed to associate with higher grade CRS [12,52,57], suggesting independent mechanisms for each process, but with overlapping risk and causative factors.

Higher peak *in vivo* proliferation of CAR T cells has been associated with CRS grade and with development with severe neurologic toxicity [8,9,13–15,20,21,25,46,52,56,58]. Determinants of both CAR T-cell expansion and toxicity include patient-specific factors and treatment-related factors.

In terms of treatment-related factors, higher cell doses and conditioning chemotherapy containing fludarabine have been associated with development of severe CRS and with

neurotoxicity [9,20,52, 56–58]. The addition of lymphodepleting chemotherapy or radiation has been shown to increase the efficacy of adoptively-transferred T cells in mice, and clinical results strongly suggest that lymphocyte-depleting chemotherapy enhances the activity of CAR T cells in humans [59–62]. Possible mechanisms for this enhancement include increasing levels of certain cytokines, such as interleukin-15, and depletion of T regulatory cells. Multiple chemotherapy regimens have been used in CAR T-cell trials. These regimens include varying doses of cyclophosphamide alone [9–11,13,15,20,63], fludarabine and cyclophosphamide [8,9,12,13,15, 18–22,25,57], pentostatin and cyclophosphamide [14], bendamustine-based regimens [14,26], as well as several disease-specific regimens determined by physician discretion [7,14,26]. The addition of lymphodepletion chemotherapy has been anecdotally shown to increase persistence of CAR T cells [63]. No one regimen has been clearly shown to be superior in terms of efficacy in optimizing CAR T-cell activity, or clearly more toxic than another. The addition of fludarabine to a regimen of cyclophosphamide alone may increase peak blood levels and persistence of CAR T cells [9], response rates [20], rates of CRS [20], and neurotoxicity [20], for the given cell product; though these effects have not been observed in all studies in which both regimens have been used [13]. Our institutional preference is for a cyclophosphamide and fludarabine conditioning regimen [29].

In terms of patient-specific factors, ALL rather than NHL, higher burden disease, baseline thrombocytopenia, and baseline elevated markers of endothelial activation, such as angiopoietin-2 (ANG2) and von Willebrand factor, have been associated with the development of severe CRS and severe neurotoxicity [7–9,11,13,15,26,52,56,58,64]. Higher burden malignancy involvement in the bone marrow has been established as a risk factor for toxicity in both patients with B-cell malignancies receiving anti-CD19 CAR T cells [58] and in patients with multiple myeloma receiving anti-BCMA CAR T cells [29,30]. ANG2 is elevated in the blood of patients with severe CRS and in patients with severe neurologic toxicity, suggesting that endothelial activation is an underlying process in both [52,56,58]. Patients with severe CRS and with severe neurologic toxicity may demonstrate signs of consumptive coagulopathy, with elevated markers of disseminated intravascular coagulation (DIC), including elevated PT, PTT, D-Dimer, and low fibrinogen [46,52,56,58]. Risk-adapted dosing of CAR T cells, with lower cell doses given to patients with higher disease burden, may ameliorate toxicity [9,13], possibly without compromising efficacy, as higher malignancy burdens may cause greater antigen stimulation, resulting in adequate CAR T-cell proliferation to induce remissions. Such risk-adapted approaches should be further prospectively evaluated.

Severe neurologic toxicity is associated with higher peak blood CRP, early peak of IL-6, and higher blood levels, at peak or at the third day following cell infusion, of multiple serum cytokines and other proteins: IL-2, sIL-2Rα, IL-6, IL-8, IL-10, IL-15, INF-ϒ, TNF-α, granzyme B, soluble GM-CSF, and MCP-1, among others [9,15,20,21,25,52,56]. Severe neurologic toxicity is also correlated with elevated CSF protein after cell infusion, possibly reflecting enhanced CSF permeability [52,56], and patients with neurologic toxicity have significantly elevated levels of multiple cytokines in the cerebrospinal fluid (CSF) [8,52,56]. In this state of blood-brain-barrier breakdown, CAR T cells are known to penetrate the CSF [8,19,21,52,56], and may in part be responsible for driving higher levels of cytokines in the

CSF compared with the blood [52]. Models to predict development of severe CRS and neurologic toxicity based on serum cytokine levels early after cell infusion have been developed and may in the future guide early intervention with immunosuppression in high risk patients [9,46,52,56,58]; however, limited availability of cytokine profiles in real-time is currently a barrier to routine use.

The structure of the chimeric antigen receptor may contribute to patterns of toxicity. CARs with costimulatory domains have increased efficacy compared to first-generation CARs [3,49,65]. CRS has been observed to begin earlier when CAR T-cell products with a CD28 costimulatory domain are administered, compared with CAR T-cell products with a 4–1BB costimulatory domain [43], and cell products with a 4–1BB costimulatory domain might have greater persistence [66]. Neurotoxicity with T cells expressing CD28-containing CARs [21,25] and deaths from cerebral edema in the ROCKET trial, which evaluated a CAR with a CD28 domain [53], have raised the question of whether CARs with a CD28 costimulatory domain pose additional risk of severe neurotoxicity. However, there is no conclusive evidence of a direct link between costimulatory domain and neurologic toxicity. Cerebral edema has been reported with CARs containing a 4–1BB costimulatory domain [15]. Neurologic toxicity in a trial of a CAR utilizing a CD28 costimulatory domain for pediatric ALL was favorably low [8]. It is also possible that the CD28 hinge and transmembrane domains, rather than the costimulatory domain alone, may be significant contributors to development of toxicity, as CARs with CD28 hinge and transmembrane domains have increased production of cytokines compared with CARs with the same single chain variable region and CD8 hinge and transmembrane domains [67]. An anti-CD19 CAR T-cell product with a CD28 costimulatory domain and CD8 hinge and transmembrane region was observed to have an incidence of Grade 3–4 neurologic toxicity of just 5% [68].

It is unclear if the antigen target of the CAR affects rate of CRS or neurologic toxicity. Information is limited as there has been substantially less experience with CARs targeting antigens other than CD19. A report of anti-CD22 CAR T cells used to treat ALL demonstrated a favorable toxicity profile, with comparatively low rates of CRS and neurologic toxicity [69]. Anti-BCMA CAR T cells have been shown in some instances to cause severe and sometimes life-threatening CRS, similar to anti-CD19 CAR T cells [29,30,70]. Severe neurologic toxicity appears overall less frequent following anti-BCMA CAR T cells [30,70], though non-fatal cerebral edema following anti-BCMA CAR T cells has been reported [70]. The mechanism of these slight differences in toxi-city profiles, and whether they are related to target antigen or to other structural differences in the CARs, is unknown.

Preclinical models of CRS and neurologic toxicity have historically been limited. However, in the last year, mouse models of CRS and neurologic toxicity have been developed [71–73], which have allowed *in vivo* assessment of the efficacy of different immunosuppressive agents against toxicity [72,73]. A rhesus macaque model of CRS and neurologic toxicity, using autologous CD20-targeting CAR T cells, has demonstrated CAR T-cell penetration into the CSF and brain parenchyma, as well as elevated CSF cytokines, very similar to what is observed in humans experiencing neurologic toxicity following CAR T-cell infusion [74].

These animal models will likely be valuable tools in improving our understanding of these toxicities, and in developing better treatment and prevention strategies.

4. CAR T-cell toxicity grading systems

Multiple systems have been used to grade CRS and neurologic toxicity (Table 2). A consensus group grading system published by Lee and colleagues in 2014 first attempted to provide a unified grading system for CRS [42]. The Memorial Sloan Kettering Cancer Center (MSKCC), the University of Pennsylvania, and the CAR-T-cell therapy-associated toxicity (CARTOX) Working Group (CARTOX group) have also published their own grading systems for CRS [11–14,43]. However, the grading systems differ in multiple aspects (Table 2). Hypo-tension is an important component of CRS grading in all systems, but hypotension with requirement of a single vasopressor may be Grade 2 in the 2014 Consensus Group and CARTOX systems, but may be Grade 3–4 in the University of Pennsylvania or MSKCC systems. Hypoxia likewise is incorporated in all four systems, but hypoxia requiring low-dose nasal cannula may be Grade 3 in the University of Pennsylvania system, while it is Grade 2 in the other three systems. Organ toxicity as graded by the Common Terminology Criteria for Adverse Events (CTCAE) is included in all systems, except for the MSKCC system, which includes only pulmonary status and hemodynamic parameters.

In recent years, neurotoxicity has come to be better understood as a related but separate process from CRS, and centers have been grading it separately. Many centers use the CTCAE system for grading of neurologic toxicity. The CARTOX consensus group have published a grading system for CAR T-cell neurologic toxicity [43]. This model includes a 10-point scoring system that assesses cognitive tasks such as orientation, naming, writing and counting backwards [43]. Cognitive scores determine neurotoxicity grade. Seizures, new motor weakness, and papilledema result in a neurotoxicity grade of 3–4 regardless of cognitive assessment score [43]. The Pediatric Oncology Group at the NCI and colleagues have developed their own grading system for neurologic toxicity, incorporating a brief computerized cognitive test and an observer-reported checklist [75]. Universal grading systems for CRS and for neurotoxicity are greatly needed as they would allow comparisons among trials of toxicities of different CAR T-cell products. Cell products with similar efficacy may be differentiated only by their toxicity profiles, making accurate comparisons of toxicity grades essential. Frequencies of high grade toxicities for various CAR T-cell products are outlined in Table 3.

5. Management approaches for CAR T-cell toxicity across institutions

Guidelines for supportive care for hospitalized patients following CAR T-cell infusion are similar with minor variations among treatment centers, with an emphasis on frequent vital signs, neurologic assessment, and frequent monitoring of blood counts, electrolytes, coagulation assays, and inflammatory markers [41,43]. However, there is variability among centers and among cell products as to preference of administering the product on an inpatient or outpatient basis. Tisagenlecleucel has been administered in clinical trials in both an inpatient and an outpatient setting [12], while axicabtagene ciloleucel was administered

to clinical trial patients exclusively in an inpatient setting [22,43]. It is unclear if these differences are due to institutional preferences or are a reflection in differences in the toxicity profiles of the cell products. Patients being monitored as outpatients following CAR T-cell therapy should be counseled to monitor their temperature and present for medical attention immediately if they are febrile [64]. Patients who present with hypotension or neurologic toxicity should be triaged early for close inpatient monitoring.

In contrast, thresholds for administering immunosuppressive drugs and doses of these agents vary greatly among centers. The IL-6 receptor antagonist tocilizumab has been widely used to treat severe CRS [7,11,14,26,29] and is FDA approved for this indication [76]. Tocilizumab has in many cases resulted in rapid and complete resolution of hemodynamic instability [7,26,46]. However, there are possible drawbacks to tocilizumab use. Tocilizumab has been shown to confer increased risk of cytopenias and infections in patients with rheumatoid arthritis [77]; whether these effects are relevant in patients receiving tocilizumab for CRS is unknown. Tocilizumab may hypothetically increase the incidence and severity of neurologic toxicity, as neurologic toxicity has anecdotally been observed to occur shortly after tocilizumab administration [42]. CRS in some instances may resolve spontaneously even when tocilizumab is not administered [18,19,21]. Conversely, in some cases, tocilizumab administration does not ameliorate CRS [29,30]. Many patients receiving tocilizumab went on to obtain complete remissions of their malignancies [7,11], but subtle impairment of anti-malignancy responses by tocilizumab has not been completely ruled out, especially if tocilizumab is given early after T-cell infusion. Despite these drawbacks, tocilizumab clearly has a role in toxicity management, and its use should not be withheld in cases of moderate to severe CRS in favor of awaiting spontaneous improvement. It should also be noted that in many cases of severe CRS additional immunosuppression with corticosteroids is needed.

In a retrospective analysis, pediatric ALL patients treated with tocilizumab and low-dose dexamethasone for persistent fevers, requirement for supplemental oxygen, or hypotension not responsive to an initial fluid bolus had no change in rates of complete remission compared to patients who received immunosuppression only for occurrence of dose-limiting toxicity, suggesting that a pre-emptive immunosuppression approach may not compromise anti-malignancy activity [78]. This is consistent with the finding in xenograft mouse models that administration of tocilizumab did not affect CAR T-cell cytotoxicity [79]. A randomized clinical trial of early *versus* late immunosuppression would clarify the effects of tocilizumab on toxicity resolution and duration of malignancy response. A clinical trial of earlier tocilizumab administration for children with higher bone marrow burden of ALL is ongoing (NCT02906371).

In some clinical trials of CAR T cells, a substantial proportion of patients received corticosteroids in addition to tocilizumab for treatment of CRS, demonstrating that anti-IL-6 targeting immunosuppression does not resolve CRS in all instances [7,8,14,20,22,28,30,47]. Corticosteroids have established efficacy in treating CRS [7,11,14]; but because corticosteroids might impair CAR T-cell activity [11], especially at high doses; they are usually reserved for refractory CRS not responding to tocilizumab [11,14,42,64]. Controversy exists as to whether corticosteroids should be initiated for any higher-grade

CRS, before response to tocilizumab has been assessed [43,64]. However, in retrospective reviews, patients receiving corticosteroids for immunosuppression have had similar anti-malignancy responses [25,57]; effects on long-term remission durability are undetermined. Other monoclonal antibodies which have been less thoroughly studied in treating CRS include siltuximab [15], infliximab [42], and etanercept [9,42]. Mouse models suggest that inducible nitric oxide synthase (iNOS), and IL-1, an inducer of iNOS, significantly contribute to CRS development, and are both potentially targets for toxicity management with inhibitors of iNOS and IL-1 [73]. Multiple groups have demonstrated the successful use of the IL-1 antagonist anakinra to ameliorate CRS in mouse models [72,73]. In cases of HLH occurring with CRS, the addition of etoposide may be considered if toxicity does not improve with tocilizumab or corticosteroid immunosuppression [43].

Tocilizumab has been observed to have limited efficacy in resolving neurologic toxicity [9,52,56], possibly because CAR T cells and inflammatory cytokines are known to cross the blood-brain barrier, but tocilizumab has poor CNS penetration [80]. For this reason, at some centers corticosteroids are the first-line therapy for isolated neurologic toxicity, with anti-IL-6 therapy given for concurrent CRS [21,25,42,43], though thresholds for administration and dosing schemas vary and have not been prospectively compared. Preclinical models suggest that anakinra may also have activity in managing neurotoxicity [72].

Suicide genes, such as truncated epidermal growth factor receptor and inducible caspase 9, have been investigated as a method of effecting abrupt cessation of CAR T-cell toxicity [81–87]. Administration of antibody or small dimerizer molecule agents induces apoptosis of cells transduced with the transgene [82,83]. A disadvantage of these systems is a corresponding abrogation of anti-malignancy efficacy, so these systems may be most appropriately used in cases of life-threatening toxicity not controlled with immunosuppression, or in the setting of ongoing long-term toxicities occurring when malignancy remission has already been achieved. These systems have been shown to be effective at eliminating CAR T cells in *in vivo* mouse models [81,83,86,88]. Suicide systems have been shown in clinical trials to deplete alloreactive T cells following allogeneic stem cell transplant [83], though robust clinical data of these systems for CAR T-cell therapy are lacking.

6. Recommendations for management of CAR T-cell toxicities

The initial evaluation and management of patients experiencing CAR T-cell related toxicity and supportive care guidelines used by the authors when treating adult patients at the National Cancer Institute are summarized in Table 4. Our guidelines for administering immunosuppression for toxicity are summarized in Fig. 1. These guidelines are written for adult patients and are not meant to be applied to pediatric patients. Because CAR T cells are a new therapy and because different CAR T-cell treatment regimens are associated with somewhat different toxicities, definitive, generally applicable treatment recommendations cannot be given. We are providing treatment recommendations based mainly on the published experience of others and on our own experience treating leukemia, lymphoma and multiple myeloma patients [7,8,11,19,21,29,30,41,42,45].

An important component of toxicity management is a baseline patient evaluation, to ensure the patient will not be exposed to inordinate toxicity due to the patient's underlying comorbidities. We proceed with CAR T-cell therapy only for patients with close to normal end organ function, including pulmonary, renal, hepatic function, and cardiac function, with a requirement for a normal cardiac ejection fraction, as previously described [41], due to concerns about patient safety. The larger published clinical trials of the FDA-approved CAR T-cell products have in large part excluded patients with baseline active CNS involvement with malignancy [12,25], such that the safety of these products for patients with CNS malignancy has not been fully explored. For this reason, we do not administer CAR T-cell therapy to patients with active CNS involvement with malignancy. Similarly, we do not offer CAR T-cell therapy to patients with a history of epilepsy, even if it is well-controlled.

In terms of patient monitoring, we hospitalize patients for monitoring prior to their CAR T-cell infusion and monitor hospitalized patients for at least 9 days following cell infusion. Baseline laboratory evaluation should include a complete blood count with differential (CBC), comprehensive metabolic panel (CMP), coagulation studies, CRP, lactate dehydrogenase (LDH), uric acid, and ferritin (Table 4). We recommend drawing a laboratory evaluation including a CBC, CMP, coagulation studies, CRP, LDH, and uric acid at least daily, though some patients may require more frequent lab analyses for cases of electrolyte wasting, coagulopathy, or need for transfusion support. When patients are discharged from the inpatient service, they continue monitoring for toxicity on an outpatient basis. Patients are instructed to monitor their temperature twice a day and present for immediate evaluation if they have a fever, as described above. Patients are counseled to monitor for neurologic toxicity, and patients are mandated to have a caregiver to assist in monitoring, and to assist in seeking medical attention for the patient if any encephalopathy develops.

According to our institutional guidelines (Table 4), any patient for whom there are concerns of developing CRS or other toxicity undergoes an initial evaluation including a complete set of vital signs, with temperature and oxygen saturation by pulse oximetry. The review of systems and physical exam focuses on the pulmonary, cardiovascular and neurologic organ systems, and should survey for occult infection. A CRP more elevated than a prior value may be a marker of escalating CRS. Patients with fevers have blood and urine cultures drawn and undergo targeted imaging based on symptoms to evaluate for infectious sources. All patients with tachycardia undergo an ECG to assess for arrhythmia. Patients with hypotension or persistent tachycardia undergo an echo-cardiogram to evaluate for decreased ejection fraction. All patients experiencing neurologic toxicity have urgent imaging of the brain with a head CT, followed by an MRI when it is available and once the patient is stable for the study. Patients with seizures or any severe neurologic toxicity should receive dexamethasone by IV push. This should not be delayed in order to obtain imaging studies. Supportive care for patients experiencing toxicity includes volume resuscitation, vasopressors as needed, transfusion support, growth factors, electrolyte repletion, and empiric broad spectrum antibiotic therapy in select patients. Due to the potential for capillary leak and pulmonary edema following CAR T-cell therapy, intensivists managing hypotension may need to transition from intravenous fluid support to vasopressor support more quickly than would be necessary for a patient experiencing hypotension from other causes. Optimized supportive care for patients experiencing CAR T-cell toxicity requires

multidisciplinary training and awareness. This includes involvement of nursing staff, intensivists, pharmacist, and emergency department staff, to identify patients experiencing toxicity and intervene in a timely manner.

Our indications for tocilizumab include hypotension requiring >5 μg/min norepinephrine or equivalent, hypoxia requiring $FiO_2 \geq 40\%$, cardiac ejection fraction decrease to < 45%, significant dyspnea, and coagulopathy (Fig. 1). As CRS can sometimes be refractory to tocilizumab, and toxicities may not be reversible in later stages, we administer high-dose corticosteroids immediately for toxi-cities such as a severe reduction in cardiac ejection fraction, dyspnea making mechanical ventilation likely, or hypotension that does not improve with vasopressors.

Our management of a patient experiencing neurologic toxicity is summarized in Fig. 1. Patients having seizures, potential airway compromise due to mental status changes, or any neurologic toxicity precluding activities of daily living (ADLs) should receive corticosteroid therapy. Immunosuppression should be continued until life-threatening toxicities have resolved and the patient can function independently.

7. Future considerations

The CAR T-cell field is still quite new, and, likewise, the management of CAR T-cell toxicities is in its early stage. Toxicity management is certain to change significantly in the coming years as more data become available. The development of universal grading scales for CRS and neurologic toxicity is an essential step in building generalizable guidelines for managing toxicity. Risk-adapted strategies for tailoring CAR T-cell dose based on malignancy burden and expected *in vivo* antigen stimulation should be evaluated prospectively in larger numbers of patients. Different clinical thresholds for administering immunosuppression should be evaluated, ideally in a randomized setting, to clarify if more liberal use of immunosuppressive agents has any effect on long-term remission rates.

Research priorities include achieving a better mechanistic understanding of the role of cytokines and other inflammatory proteins in mediating toxicity. Improved animal models of CAR T-cell toxicity will likely prove valuable in addressing this research question. Cytokine panels that can be used in real-time to predict severity of toxicity and to direct intervention with immunosuppression in select patients should be further developed. Alternative immunosuppressive agents, other than tocilizumab and corticosteroids, are likely to have increasing clinical use as our understanding of the mechanisms of toxicity improve. Additionally, preclinical studies are hoped to lead to the development of optimal CAR structures that minimize toxic effects while maintaining efficacy. The development of later-generation CARs, which may incorporate multiple costimulatory domains or enable the transduced T cell to secrete specific cytokines, may enhance anti-malignancy efficacy, but may also alter expected toxicity profiles [3,89]. CAR T-cell therapy is increasingly evaluated for use in solid tumor malignancies. Malignancy-associated antigens of solid tumors may in some cases be more widely expressed on normal tissues, which may increase the likelihood of CAR-mediated damage to essential normal cells [6,89,90].

8. Conclusions

CAR T-cell therapy is a great advance in the treatment of hematologic malignancies. While CRS and neurologic toxicity remain barriers to widespread use of this therapy, improved understanding of the pathophysiology of these processes will aid in the development of optimum strategies of immunosuppression and supportive care.

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1.

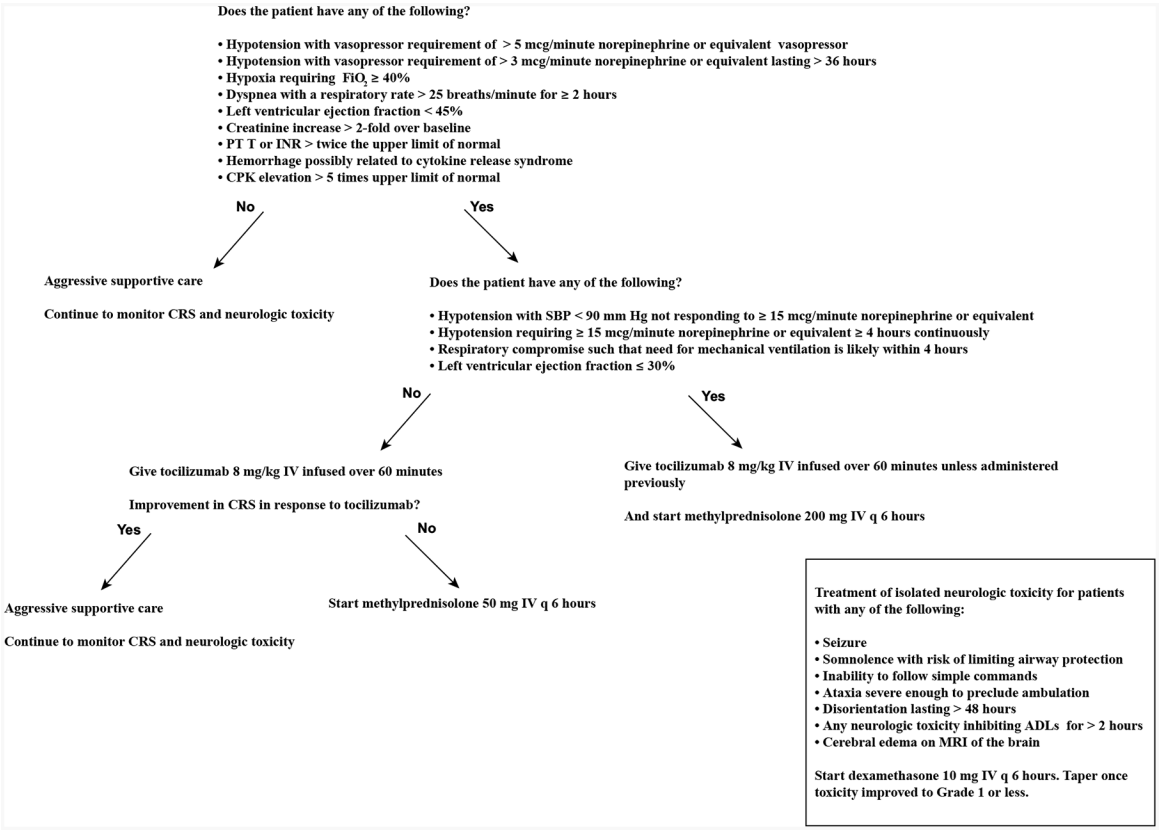
Practice Points

- Mild to moderate CRS and neurologic toxicities may resolve without intervention with immunosuppression. However, severe CRS and neurologic toxicities may be life-threatening, and may require intensive care and immunosuppressive therapy.
- Cytokine release syndrome and neurologic toxicity may not occur at the same time. Resolution of CRS does not preclude the development of neurologic toxicity.
- Patients with higher burden malignancy, especially those with higher malignancy burdens in the bone marrow, may be at increased risk of toxicity. Patients receiving higher CAR T-cell doses may be at higher risk of toxicity.
- Some CAR T-cell products may be given in the outpatient setting. Fevers in the days following CAR T-cell infusion are an indication to hospitalize patients, as fevers are often the first symptoms of developing CRS.
- Patients with neutropenic fevers or fevers with hemodynamic instability should receive broad spectrum antibiotic coverage, even if CRS is suspected as the underlying etiology.
- The IL-6 receptor antagonist tocilizumab is used as the first-line agent to manage severe CRS. However, tocilizumab does not reverse all cases of CRS.
- Corticosteroids should be administered for patients with immediately life-threatening CRS and for CRS that does not respond to tocilizumab.
- Corticosteroids are the preferred first-line immunosuppressive agent for severe neurologic toxicity.

2.

Research Agenda

- Continued improvement in preclinical animal models of CRS and neurologic toxicity.
- Development of cytokine panels that can be used in real-time to predict severity of toxicity and to direct intervention with immunosuppression in select patients.
- Randomized clinical trials to evaluate strategies of early *versus* late administration of immunosuppression for CRS.
- Prospective evaluation of risk-adapted strategies of CAR T-cell dosing to reduce toxicity while maintaining efficacy.
- Optimization of CAR T-cell structure to minimize toxicity while retaining efficacy.



. Management of severe CRS and neurologic toxicity in adults following CAR T-cell infusion. The approach to CAR T-cell toxicity management currently used in adult patients at the National Cancer Institute is shown. We administer a single dose of tocilizumab at the 8 mg/kg dose. We do not re-dose for persistent toxicity but instead move to corticosteroids in cases of persistent toxicity following tocilizumab. It is important to note that management of CRS varies among clinical trials, and some centers give tocilizumab and/or low-dose corticosteroids earlier in the course of CRS than outlined here. If the toxicities of concern do not significantly improve within hours after administration of tocilizumab, intermediate-dose corticosteroid therapy is administered. For certain severe hemodynamic toxicities, high-dose methylprednisolone is emergently administered concurrently with tocilizumab. Patients experiencing severe neurologic toxicity following CAR T-cell infusion should receive corticosteroids for immunosuppressive therapy. Imaging of the brain should not delay the administration of the first dose of corticosteroid therapy for clinically severe neurologic toxicity. These regimens have been effective to alleviate toxicities in our experience, but we do not have formal clinical trial evidence to support these regimens. In general, corticosteroids should be discontinued as soon as toxicity returns to a tolerable level. Please note that thresholds for vasopressor requirements and corticosteroid doses are based on our institutional experience and not on validated published data. ADLs: activities of daily living. CPK: creatine phosphokinase. CRS: cytokine release syndrome. FiO_2: fraction of inspired oxygen. INR: International Normalized Ratio. MRI: magnetic resonance imaging. PTT: partial thromboplastin time. SBP: systolic blood pressure.

Table 1

CAR T-cell Toxicities.

Organ system	Toxicities
Constitutional	• Fever • Fatigue and malaise • Headache
Cardiovascular	• Sinus tachycardia Hypotension • Decreased left ventricular ejection fraction • Arrhythmias • QT prolongation • Troponinemia
Respiratory	• Hypoxia Dyspnea • Increased respiratory rate Respiratory failure • Pleural effusions Capillary leak syndrome
Renal	• Increased serum creatinine • Renal insufficiency • Hyponatremia • Hypokalemia • Hypophosphatemia • Tumor lysis syndrome
Hepatic and Gastrointestinal	• Increases in liver transaminases: elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or direct bilirubin • Nausea, vomiting • Diarrhea
Hematologic	• Anemia • Thrombocytopenia • Neutropenia • B-cell aplasia Hypogammaglobulinemia • Prolongation of partial thromboplastin time (PTT) or prothrombin time (PT) • Decreased fibrinogen • Disseminated intravascular coagulation (DIC) Hemophagocytic lymphohistiocytosis
Immunologic	• Risk of viral infections • Risk of bacterial infections • Risk of fungal infections
Musculoskeletal	• Creatine phosphokinase (CPK) elevation • Myalgias
Neurologic	• Delirium, encephalopathy • Somnolence, obtundation

Organ system	Toxicities
	• Cognitive disturbance
	• Dysphasias
	• Tremors
	• Ataxia
	• Myoclonus
	• Focal motor and sensory defects
	• Seizures
	• Cerebral edema

Table 2

Comparison of cytokine release syndrome (CRS) grading systems.[a]

CRS Grade	Consensus Group [42]	University of Pennsylvania [14]	Memorial Sloan Kettering Cancer Center [13]	CARTOX Working Group [43]
Grade 1	• Symptoms are not life threatening and require symptomatic treatment only, *e.g.,* fever, nausea, fatigue, headache, myalgias, malaise	• Mild reaction, treated with supportive care	• Mild symptoms requiring observation or symptomatic management only	• Temperature ≥ 38.0 °C • SBP ≥ 90 mmHg • No oxygen required for $Sa0_2$ > 90% • Grade 1 organ toxicities
Grade 2	• Symptoms require and respond to moderate intervention • Hypotension responsive to IV fluids or a low dose of a single vasopressor, not meeting criteria for grade 3 • Oxygen requirement < 40% $Fi0_2$ • Grade 2 organ toxicity	• Hospitalization indicated – IV therapy – neutropenic fevers – parenteral nutrition • Grade 2 creatinine increase • Grade 3 LFT increase	• Moderate symptoms • Hypotension requiring any dose of vasopressors • < 24 h, not meeting criteria for grade 3–4 • Hypoxia or dyspnea requiring supplemental oxygen, • < 40%, up to 6 Liters by nasal cannula	• Hypotension with SBP < 90 mmHg, responding to IV fluids or vasopressors, at doses not meeting criteria for grade 3 • Hypoxia requiring supplemental oxygen, $Fi0_2$ < 40% • Grade 2 organ toxicities
Grade 3	• Symptoms require and respond to aggressive intervention • Hypotension requiring multiple vasopressors or high dose vasopressors as defined: – norepinephrine ≥ 20 μg/min – dopamine ≥ 10 μg/kg/min – phenylephrine ≥ 200 μg/min – epinephrine ≥10 μg/min – vasopressin + norepinephrine ≥ 10 μg/min – other vasopressor dose equivalent to	• Hypotension requiring IV fluids or low-dose vasopressors, defined as not meeting criteria for grade 4 • Hypoxia requiring supplemental 0_2, including CPAP/BiPAP • Coagulopathy requiring FFP or cryoprecipitate • Grade 3 creatinine increase • Grade 4 LFT increase	• Severe symptoms • Hypotension requiring any vasopressors ≥ 24 h, not meeting criteria for grade 4 • Hypoxia or dyspnea requiring supplemental oxygen ≥ 40%	• Hypotension requiring multiple or high dose vasopressors, as defined: – norepinephrine ≥20 μg/min – dopamine ≥ 10 μg/kg/min – phenylephrine ≥ 200 μg/min – epinephrine ≥ 10μg/min – vasopressin + norepinephrine – ≥ 10 μg/min – other vasopressor dose equivalent to norepinephrine ≥ 20 μg/min

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CRS Grade	Consensus Group [42]	University of Pennsylvania [14]	Memorial Sloan Kettering Cancer Center [13]	CARTOX Working Group [43]
	norepinephrine ≥ 20 μg/min • Oxygen requirement ≥ 40% FiO_2 • Grade 3 organ toxicity • Grade 4 transaminitis			• Hypoxia requiring supplemental oxygen ≥ 40% • Grade 3 organ toxicities or Grade 4 transaminitis
Grade 4	• Life-threatening symptoms • Requirement for ventilator support • Grade 4 organ toxicity (excluding transaminitis)	• Hypotension requiring high dose vasopressors defined as: – norepinephrine ≥ 0.2 μg/kg/min – dopamine ≥ 10 μg/kg/min – phenylephrine ≥ 200 μg/min – epinephrine ≥ 0.1 μg/kg/min – other vasopressor dose equivalent to norepinephrine ≥0.2 μg/kg/min • Hypoxia requiring mechanical ventilation • Life-threatening toxicity	• Life threatening symptoms • Hypotension refractory to vasopressors with failure to reach target blood pressure despite use of vasopressors of the listed doses for ≥ 3 h – norepinephrine ≥20 μg/min – dopamine ≥ 10 μg/kg/min – phenylephrine ≥200 μg/min – epinephrine ≥ 10 μg/min – other vasopressor dose equivalent to norepinephrine ≥ 20 μg/min • Hypoxia or dyspnea requiring mechanical ventilation	• Hypotension that is life-threatening • Requirement for ventilator support • Grade 4 organ toxicity (excluding transaminitis)

Bi-PAP: bilevel positive airway pressure. CPAP: continuous positive airway pressure FFP: fresh frozen plasma. FiO_2: fraction of inspired oxygen. LFT: liver function tests (transaminases). SBP: systolic blood pressure.

[a] Unless otherwise indicated, the presence of any clinical criterion indicated by a bullet point results in classification as the listed Grade CRS.

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Table 3

Toxicity profiles of select CAR T-cell products.

Cell product	Malignancy	Cell doses	ORR and CR rate (%) Deaths (absolute number)*	CRS (%)	Neurotoxicity (%)
Tisagenlecleucel					
Maude et al. [12], *n* = 75	Pediatric ALL	0.2×10^6 to 5.4×10^6 CAR+ cells /kg	MRD neg CR: 81 Deaths: 0	All[P]: 77 Grade 3–4: 46	All: 40 Grade 3–4: 13
Schuster et al. [28], *n* = 99	DLBCL	$0.1–6 \times 10^8$ CAR+ cells	ORR 53 CR 40 Deaths: 0	All[P]: 58 Grade 3–4: 23	All: NR Grade 3–4: 12
Schuster et al. [26], *n* = 28	NHL	$1.79–5 \times 10^8$ CAR+ cells	DLBCL: ORR 50 CR 43 FL: ORR 79 CR 71 Deaths: 1	All[P]: 57 Grade 3–4: 18	All: 39 Serious: 11**
Fraietta et al. [17]; *n* = 41 (reports antimalignancy responses) Porter et al. [14], *n* = 14 (reports toxicity)	CLL	1.5×10^7-5×10^9 total nucleated cells	ORR 39 CR 20 Deaths: 0	All[P]: 64 Grade 3–4: 43	All: 36 Grade 3–4: 7
Axicabtagene ciloleucel					
Lee et al. [8], *n* = 21	Pediatric ALL	$0.03–3 \times 10^6$ CAR+ cells /kg	CR 70 MRD neg CR 60 Deaths: 0	All[L]: 76 Grade 3–4: 29	All: 29 Grades 3–4: 5
Kochenderfer et al. [18] Kochenderfer et al. [19] Kochenderfer et al. [21] *n* = 45	NHL and CLL	$1–30 \times 10^6$ CAR+ cells/kg	ORR 81 CR 50 Deaths: 2	All: NR Grade 3–4: NR	All: NR Grade 3–4: 44
Locke et al. [22]	Aggressive NHL	2×10^6 CAR+ cells /kg	ORR 80	All[L]: 93	

Cell product	Malignancy	Cell doses	ORR and CR rate (%) Deaths (absolute number)*	CRS (%)	Neurotoxicity (%)
Neelapu et al. [25]			CR 55		All: 67
n = 108			Deaths: 3	Grade 3–4: 12	Grade 3–4: 30
lisocabtagene maraleucel; JCAR017					
Abramson et al. [27], *n* = 91	Aggressive NHL	≤1 × 10^8 CAR+ T cells	ORR 74	All[L]: 35	All: 19
			CR 52	Grade 3–4: 1	Grade 3–4: 12
			Deaths: 0		
Fred Hutchinson Cancer Center CAR T-cell product					
Turtle et al. [9], *n* = 30	Adult ALL	2 × 10^5-2 × 10^7 CAR+ T cells /kg	MRD neg CR 86	All: 83	All: 50
			Deaths: 2	Serious: 23[^]	Grade 3–4: 47
Turtle et al. [20], *n* = 32.	NHL	2 × 10^5-2 × 10^7 CAR+ T cells /kg	All patients:	All[L]: 63	All: 25
			ORR 63	Grade 3–4: 22	Grade 3–4: 22
			CR 33		
			Flu/Cy conditioning:		
			ORR 72		
			CR 50		
			Deaths: 2		
Turtle et al. [15], *n* = 24	CLL	2 × 10^5-2 × 10^7 CAR+ T cells /kg	ORR 74	All[L]: 83	All: 33
			CR 21	Grade 3–4: 4	Grade 3–4: 21
			Deaths: 1		
1928z CAR T					
Park et al. [13], *n* = 53	Adult ALL	1– 3 × 10^6 CAR+ T cells/kg	CR 83	All[MSK]: 85	All: NR
			MRD neg CR 67	Grade 3–4: 25	Grade 3–4: 42
			Deaths: 1		

Abbreviations: ALL: acute lymphoblastic leukemia. CLL: chronic lymphocytic leukemia. CR: complete response. DLBCL: Diffuse Large B-cell lymphoma. FL: follicular lymphoma. MRD neg CR: minimal residual disease negative complete response. NHL: Non-Hodgkin lymphoma. ORR: overall response rate. NR: not reported. Ped ALL: Pediatric acute lymphoblastic leukemia. TM: transmembrane domain.

*Deaths due to any cause other than progressive malignancy.

**The percent of neurologic events categorized as serious was 11% in the single center report of tisagenlecleucel in NHL (Schuster et al., 2017).

^ Serious defined as requiring intensive care and treatment with immunosuppression.

P CRS graded according to the University of Pennsylvania grading system.

L CRS graded according to the grading system described by a Consensus Group in Lee et al., (2014).

MSK CRS graded according to the Memorial Sloan Kettering Grading System.

Table 4

Initial evaluation of a patient experiencing toxicity following CAR T-cell infusion.

Assessment category	Evaluation	Supportive care interventions based on assessment
History	• Constitutional symptoms • Infectious disease review of systems • Neurologic review of systems	• Acetaminophen and cooling blankets for fevers or rigors
Physical exam	• Full set of vital signs, including pulse oximetry • Full neurologic exam • Pulmonary exam • Cardiovascular exam focusing on volume status and evidence of arrhythmia	• Frequent (at least q 4 h) vital signs in hospitalized patients • Serial neurologic exams in hospitalized patients • Cardiac monitor in all tachycardic or hypotensive patients • Supplemental oxygen and continuous pulse oximetry in hypoxic patients • Maintenance IV fluids for all febrile or tachycardic patients • Bolus IV fluids and vasopressor support as needed for hypotension • Immediate antiepileptic therapy and dexamethasone 10 mg IV for any seizures
Laboratory testing[a]	• CBC with differential CMP • Magnesium • Phosphorus • PT • PTT • D-Dimer • Fibrinogen • CRP • LDH • Uric acid CPK Lactate Ferritin • Cardiac troponin in all tachycardic or hypotensive patients • Blood and urine cultures in all febrile patients • ABG in hypoxic or dyspneic patients	• Broad spectrum antibiotic coverage in febrile patients who are neutropenic or hemodynamically unstable • Aggressive electrolyte repletion of potassium, phosphorus and magnesium • Transfusion support to maintain Hb > 8g/dL and platelet count > 20 k/μL • G-CSF if ANC < 500/μL[b] • FFP and cryoprecipitate replacement in patients with significant prolongation of PT or PTT, significant decrease in fibrinogen, hemorrhage, or DIC • Aggressive hydration and consideration of rasburicase for tumor lysis syndrome and hemodialysis for severe renal failure
Imaging and other studies	• CXR if oxygen saturation < 95% or if patient dyspneic ECG if HR > 100 • Urgent head CT scan in patients experiencing neurologic toxicity	• Antiarrhythmics in patients with confirmed arrhythmias • Antimicrobials for confirmed infections • Emergent procedural intervention with subspecialty consultation in patients with hemorrhage

Assessment category	Evaluation	Supportive care interventions based on assessment
	• Brain MRI as soon as available following head CT in patients experiencing neurologic toxicity • TTEin patientswith hypotension,HR > 120, arrhythmias,or elevated cardiac troponin • Body CT imaging as needed to evaluate for concurrent infection • Lumbar puncture if safe following MRI to rule out infection in patients experiencing neurologic toxicity	• Immunosuppressive drugs in select patients with CRS or neurologic toxicity as per Fig. 1

ABG: arterial blood gas. ANC: absolute neutrophil count. CBC: complete blood count. CMP: comprehensive metabolic panel, including sodium, potassium, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, magnesium, and phosphorous. CPK: creatine phosphokinase. CRP: C-reactive protein. CRS: cytokine release syndrome. CT: computed tomography. CXR: chest x-ray. DIC: disseminated intravascular coagulation. ECG: electrocardiogram. FFP: fresh frozen plasma. G-CSF: granulocyte colony-stimulating factor. Hb: hemoglobin. HR: heart rate. IV: intravenous. LDH: lactate dehydrogenase. MRI: magnetic resonance imaging. PT: prothrombin time. PTT: partial thromboplastin time. TTE: transthoracic echocardiogram.

[a]All patients should undergo all listed laboratory evaluation as a baseline prior to the CAR T-cell infusion, with the exception of lactate, cardiac troponin, blood and urine cultures, and arterial blood gas. A B-type natriuretic peptide (BNP) may be useful in some settings.

[b]There is no standard approach to G-CSF support following CAR T-cell therapy. The risk of possible exacerbation of the CRS inflammatory response or hypothetical risk of malignancy stimulation in the case of ALL must be considered when using G-CSF.